(a) contacting a modified host cell with a test compound, wherein said modified host cell comprises:

a first fusion protein comprising an activation domain, operatively associated with the kinase-inducible domain (KID) of CREB,

C4

a second fusion protein comprising a GAL4 DNA binding domain, operatively associated with the CREB binding domain (KIX) of CBP, and

a reporter construct comprising a GAL4 response element operatively linked to a reporter gene; and

(b) selecting those test compounds which cause reduced expression of the reporter gene product, wherein said compounds are identified as disrupting a complex comprising CREB and CBP.

II. REMARKS

The presently claimed invention offers novel and nonobvious methods for treating individuals with diabetes mellitus by inhibiting the interaction between the cAMP responsive transcriptional activator CREB and CBP, a protein that binds to the phosphorylated (i.e., activated) from of CREB and mediates cAMP responsive transcription. Also claimed are methods to select such inhibitors.

Claims 1-7, 12 and 17 are pending in the case. Claims 1, 5, 12 and 17 have been amended herein. Claim 5 has been amended to correct a spelling error. Claims 1, 12 and 17 have been amended to recite that diabetes mellitus is treated in an individual. Support for the claim amendments is found throughout the specification. The amendments raise no issue of new matter.

OBJECTION TO THE CLAIMS

Claim 5 has been objected to because the "glucagon" is misspelled. Claim 5 has been suitably amended.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, first paragraph

The rejection of claims 1-7, 12 and 17 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement on two separate grounds is respectfully traversed. Reconsideration of the rejection is respectfully requested in view of the amendment and arguments below.

Ground #1:

The claims are rejected as allegedly lacking enablement because diabetes does not exist in a cell-based "biological system." Although Applicant takes issue with the basis for the rejection, in order to further prosecution of the case, the claims have been amended to recite treatment of '"an individual." Accordingly, this ground of rejection has been obviated.

Ground #2:

The claims are rejected because the specification allegedly does not provide factual evidence that a compound which inhibits or disrupts the binding of CREB to CBP is beneficial in treating diabetes mellitus. It is respectfully submitted that the Examiner's evidence is insufficient to support a prima facie rejection for lack of enablement. The basis for the rejection rests solely on the Merck Manual, 17th edition, pages 174-176, which is cited because it allegedly does not mention that inhibition of CREB-CBP interaction is a known mode of action for diabetes treatment (Office Action, p.3). It is improper, however, to rely on the Merck Manual for this purpose. The reference is merely a general resource for medical disease diagnosis and treatment. In fact, the specific citation to diabetes mellitus in the Merck Manual describes only well known therapeutic approaches (i.e., insulin, sulfonylureas, and anti- hyperglycemic drugs), some known for decades. The Merck Manual fails to mention any recent therapies for diabetes

mellitus, a good number of which have recently issued as U.S. patents [see, for example, U.S. Nos. 6,146,653 (amylin agent); 5,541,192 (substituted sulfonamides); 5,691,386 (triterpenoids); 5,674,900 (terpenoids), 5,700,795 (muscarinic receptor antagonists); and 5,561,110 (carnosine)].

Failure to be discussed in the Merck Manual is simply an insufficient basis to support a prima facie rejection over 112, first paragraph (enablement). More probative evidence on the feasibility of the claimed method may be found by resort to peer reviewed scientific publications. In this regard, Mayr et al. ("Transcriptional Regulation of the Phorphorylation-Dependent Factor CREB" Molec. Cell Biol., 2:599, 2001), attached as Exhibit A, describes that phosphorylation of Ser^{33} in CREB potentiates transcriptional activation by CREB through binding of CBP, which allows association with RNA polymerase II complexes (p.604, left col., 2nd full para., citing to refs 7, 80, 81, 72 and 82). Thus, Mayr and others demonstrate that transcriptional activation by CREB requires downstream interaction with CBP. Furthermore, Herzig et al., ("CREB Regulates Hepatic Gluconeogenesis Through the Coactivator PGC-1" Nature 413:179-183, 2001), attached as Exhibit B, demonstrates that CREB transcriptional activation plays a role in diabetes mellitus. As shown in Figure 2, CREB inhibition in *db/db* diabetic mice reduced blood glucose fasting levels to normal. Based on these and other findings, the authors conclude, as cited below, that activation by CREB (of PGC-1) contributes to the pathogenesis of type II diabetes and that disruption of the CREB-CBP interaction provides a useful therapeutic avenue to treat diabetes mellitus.

> The effect of A-CREB on liver gene expression suggests that CREB may constitute an ideal target for therapeutic intervention. Although use of a dominant negative inhibitor such as A-CREB may not be feasible in this regard, **small molecules that block CREB phosphorylation or disrupt recruitment of the CREB coactivator CBP (CREB binding protein) may prove effective**. Such compounds may be particularly beneficial as adjunctive therapy in lowering fasting blood glucose levels in type II diabetes.

Id. at p. 182 (emphasis added).

It is respectfully submitted that publication in peer-reviewed and prestigious scientific journals such as the publications by Mayr et al. and Herzig et al. is a far better indicator of

enablement that overcomes any negative inference arising from a failure to be mentioned in the Merck Manual, particularly as in the present case, where the therapy is quite new and has not yet been clinically tested. Therefore, in view of the above, the rejection of the claims for lacking enablement should be withdrawn.

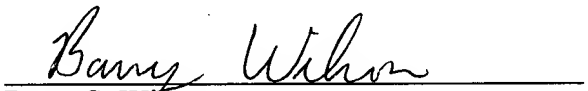
III. SUMMARY

It is respectfully submitted that the above amendments and remarks place the application in condition for allowance. Accordingly, reconsideration and favorable action on all the claims is respectfully requested. If a telephone call would further prosecution of this case, the Examiner is invited to call the undersigned attorney at (858) 847-6722.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-0872**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: September 27, 2001



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CLAIM AMENDMENTS

1. (Amended) A method for treating diabetes mellitus, said method comprising contacting an individual [a biological system] with an effective amount of a compound which inhibits binding of CREB to CBP.

5. (Amended) A method according to claim 2 wherein transcription of glucagon [glucogon] gene is inhibited.

12. (Twice Amended) A method for treating diabetes mellitus, comprising contacting an individual [a biological system] with an effective amount of a compound which disrupts a complex comprising cyclic AMP response element binding protein (CREB) and CREB binding protein (CBP), said compound identified by a method comprising:

(a) contacting a modified host cell with a test compound, wherein said modified host cell comprises:

a first fusion protein comprising a GAL4 DNA binding domain, operatively associated with the kinase-inducible domain (KID) of CREB,

a second fusion protein comprising an activation domain, operatively associated with the CREB binding domain (KIX) of CBP, and

a reporter construct comprising a GAL4 response element operatively linked to a reporter gene; and

(b) selecting those test compounds which cause reduced expression of the reporter gene product, wherein said compounds are identified as disrupting a complex comprising CREB and CBP.

17. (Amended) A method for treating diabetes mellitus, comprising contacting an individual [a biological system] with an effective amount of a compound which disrupts a complex comprising cyclic AMP response element binding protein (CREB) and CREB binding protein (CBP), said compound identified by a method comprising:

(a) contacting a modified host cell with a test compound, wherein said modified host cell comprises:

a first fusion protein comprising an activation domain, operatively associated with the kinase-inducible domain (KID) of CREB,

a second fusion protein comprising a GAL4 DNA binding domain, operatively associated with the CREB binding domain (KIX) of CBP, and

a reporter construct comprising a GAL4 response element operatively linked to a reporter gene; and

(b) selecting those test compounds which cause reduced expression of the reporter gene product, wherein said compounds are identified as disrupting a complex comprising CREB and CBP.